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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,180	NORTON, LARRY	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date August 8, 2006
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted August 11, 2006 wherein claims 1-39 are cancelled, and new claims 40-129 are introduced. This application claims benefit of provisional application 60/432840, filed December 12, 2002.

Claims 40-129 are pending in this application.

Claims 40-129 are examined on the merits herein.

Applicant's substitute drawing submitted August 11, 2006 has been fully considered and found to be acceptable to replace figure 1 submitted on December 12, 2003, as the new drawing clearly distinguishes the symbols for the various chemotherapeutic agents.

Applicant's amendment submitted August 11, 2006 with respect to the objection to instant claim 39 for not being a complete sentence, has been fully considered and found to be sufficient to remove the rejection because the aforementioned claim is no longer pending.

Applicant's amendment submitted August 11, 2006 with respect to the rejection of instant claims 38 and 39 under 35 USC 112, first paragraph for lacking enablement for a method of treating any cancer with a dose-dense therapy involving any

chemotherapeutic agent, has been fully considered and found to be sufficient to remove the rejection because the aforementioned claims are no longer pending.

Applicant's amendment submitted August 11, 2006 with respect to the rejection of instant claims 1-3, 9, 19, 23-26, 32, and 38-39 under 35 USC 102 for being anticipated by Hudis et al., has been fully considered and found to be sufficient to remove the rejection because the aforementioned claims are no longer pending.

Applicant's amendment submitted August 11, 2006 with respect to the rejection of instant claims 4-8, 10-18, 20-22, 27-31, and 33-37 under 35 USC 103 for being obvious aver Hudis et al. in view of Henderson et al., has been fully considered and found to be sufficient to remove the rejection because the aforementioned claims are no longer pending.

Applicant's amendment, submitted August 11, 2006 necessitates the following new grounds of rejection.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44, 70, 87, 97, 106, 114, and 129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted August 11, 2006 with respect to new claims 44, 70, 87, 97, 106, 114, and 129 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for the limitation, "wherein the dose-dense protocol specifies an interval of time between any two consecutive chemotherapy cycles **of less than 12 days**," in new claims 44, 70, 87, 97, 106, 114, and 129. Nothing in Applicant's specification suggests an interval of less than 12 days between chemotherapy treatments. P. 5, second paragraph specifically discloses 12-16 days as a preferred interval, while the disclosed clinical trial (pp. 8-15) uses an interval of 14 days. No protocol using a limitation of under 12 days is ever disclosed. Thus Applicant's specification does not provide adequate support for a limitation of under 12 days.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc v. Mahurkar,* 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claims 83-118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of providing chemotherapeutic treatment for breast cancer involving the specific sequential combination of drugs such

as the sequence of doxorubicin, taxane, and cyclophosphamide recited in claim 40, does not reasonably provide enablement for a method of providing chemotherapeutic treatment for any type of cancer using any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method for cancer chemotherapy which is an improvement over existing chemotherapeutic methods. The claimed invention is alleged to be an improvement over the prior art in two ways. The first improvement is the administration of the chemotherapeutic agents in a sequential dose-dense protocol, as opposed to a simultaneous combination protocol. The second alleged improvement is the administration of a specific optimized regimen of dose, frequency, and duration of treatment which is claimed to produce improved results.

The state of the prior art: The skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single

chemotherapeutic drug is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs, including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin. Breast cancer, on the other hand, is best treated with surgery and/or radiation, but the prognosis can be improved by the addition of adjuvant chemotherapy.

Dose-dense chemotherapy is well known in the prior art for the treatment of carcinomas, especially breast cancer. However, it is not widely practiced for the treatment of sarcomas or leukemias.

The relative skill of those in the art: The level of skill in the art is high.

The predictability or unpredictability of the art: As mentioned above, no single treatment is effective for all cancers. Different cancers vary widely in their response to different chemotherapy regimens. According to the Oxford Textbook of Oncology, (Reference cited in PTO-892) "The important criteria for the tumor include its sensitivity to cytostatic drugs, its clinical stage and its mass, the presence of measurable lesions or biochemical markers, and, finally, growth characteristics," as well as, "*In vitro* sensitivity tests have been disappointing. They predict well for resistance but are of little use for sensitivity," (p. 451, right column, second paragraph) and, "For many types

of cancer the potential benefit of chemotherapy has not been demonstrated in well-designed clinical trials."

Based on the known teachings of the prior art such as that stated above, one skilled in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors: gynecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CAN, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by performing the necessary experimentation to develop an optimized dose-dense protocol for treating said cancers.

Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Additionally, the claims are interpreted to apply to new drugs for which comprehensive pharmacological data, such as optimal dosages and effectiveness against specific cancers, is not yet available.

The Breadth of the claims: Instant claims 38-39 include methods for treatment or any cancer with any chemotherapeutic agent useful for the treatment of said cancer.

The only limits are that the therapy must be administered in a dose-dense protocol and that it must be more effective than treatment in a non-dose-dense protocol.

The amount of direction or guidance presented: While the specification and included references give a detailed description, both theoretical and practical, of dose-dense therapy of breast cancer, they fail to give any guidance to one skilled in the art wishing to practice the invention for other sorts of cancers, such as melanomas or leukemias. In particular, applicant's disclosure does not address whether the effectiveness of dose-dense chemotherapy against resistant tumors could be expected to extend to classes of tumors, such as hepatomas and melanomas, which are not normally responsive to chemotherapy.

The presence or absence of working examples: All of the working examples concern a single intergroup trial studying the effectiveness of sequential dose-dense chemotherapy involving doxorubicin, paclitaxel, and cyclophosphamide for the treatment of breast cancer. No working examples were given for the treatment of other cancers using other drugs.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable art such as chemotherapy. See MPEP 2164.

The quantity of experimentation necessary: In order to use the disclosed information to practice the claimed invention for a wide range of cancers using a wide range of drugs, a skilled practitioner of the art would develop a specific therapeutic regimen involving a specific combination of drugs for each chemotherapy-responsive cancer. This would involve a process of optimizing and testing various regimens *in vivo*

for each type of cancer being treated. This process would involve unpredictable experimentation which would constitute an undue experimental burden on the practitioner.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the unpredictability of the art and the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all types of cancer.

Response to Argument:

Applicant's arguments submitted August 11, 2006 with respect to the rejection of former claims 38-39 on the same grounds have been fully considered and have not been found to be persuasive to overcome the rejection of instant claims 83-118 under 35 USC 112.

Applicant argues that the establishment of a dose-response curve for a particular chemotherapeutic agent against a particular cancer is absolutely routine and involves no unpredictable experimentation. Furthermore, Applicant argues that it is well known which drugs are useful against which cancers, so that, faced with a particular cancer, one skilled in the art would be able to choose the appropriate drugs with which to treat the cancer.

However, as the extremely broad scope of Applicant's invention is drawn to each and every possible combination of a tumor and one or more chemotherapeutic agents, regardless of whether or not said combinations are known to be functional. For example, the scope of the claims includes a method of treating a drug-resistant tumor with a drug to which it is resistant, or treating a tumor with a class of drug which is not recognized as being useful for that kind of tumor. Therefore Applicant is not enabled for each and every embodiment of the claimed invention.

For these reasons the argument is not found to be convincing. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL**.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-43, 45-69, 70-86, 88-96, 98-105, 107-113, and 115-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudis et. al. (Reference included with PTO-1449, marked as reference "A" by examiner), in view of Henderson et al. (reference included with PTO-892).

Hudis et. al. describes a course of sequential dose-dense chemotherapy using the same three drugs specified by the claimed invention. In particular, p. 20, Fig. 1

illustrates the course of treatment used, which consisted of three doses of Doxorubicin, separated by 21 weeks (14 days) each, three doses of Paclitaxel separated by 2 weeks each, and three doses of cyclophosphamide separated by 2 weeks each. The same course of treatment is described on p. 19 left column, under the heading *Treatment Plan*. Furthermore, the same paragraph mentioned above (p. 18, left column, *Treatment Plan.*) also discloses that, "All nine cycles of chemotherapy were supported by granulocyte colony stimulating factor, 5 μg/kg subcutaneously, administered on days 3 through 10." Hudis et al. does not teach the specific doses of 60, 175, and 600 mg/m^2 for doxorubicin, paclitaxel, and cyclophosphamide mentioned in the aforementioned claims, nor does Hudis et. al. teach the administration of said chemotherapy agents in four cycles or in an order other than doxorubicin first, paclitaxel second, and cyclophosphamide third.

Henderson et al. describes a study (CALGB 9344) comparing several chemotherapy regimens involving Doxorubicin, Paclitaxel, and Cyclophosphamide. These drugs were administered in amounts of 60, 75, and 600 mg/m^2 in four cycles each. Furthermore, the study concluded that escalation of the dose of doxorubicin produced no additional benefit.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Hudis et. al. by reducing the dosage of the drugs used and increasing the number of cycles in each treatment, as well as by administering the three drugs in the various orders disclosed in instant claims 120-125.

One of ordinary skill in the art would have been motivated to do so in order to avoid administering an excess of these toxic drugs by reducing the dose and to ensure complete eradication of cancer cells by adding a fourth cycle to each treatment, particularly in view of the teaching of Henderson et al. disclosing that lower doses of these drugs are equally effective. One of ordinary skill in the art would have been motivated to administer the drugs in a different order because the neither Hudis et al. nor any other prior art discloses any reason to believe that the order in which the drugs are administered effects the treatment outcome.

One of ordinary skill in the art would have reasonably expected success because the reduced doses and increased number of cycles were already known to be effective for the treatment of breast cancer, and because the treatment regimen of the instant invention differs only slightly from that of Hudis et al. Furthermore, determination of exact treatment regimens, including exact dosage, duration of treatment, and order of administration of various drugs, is within the ordinary skill in the practice of medicine.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument:

Applicant's arguments submitted August 11, 2006 with respect to the rejection of similar claims on the same grounds have been fully considered and have not been found to be persuasive to overcome the rejection of instant claims 40-129 under 35 USC 103.

Applicant asserts that one of ordinary skill in the art would not have been motivated to reduce the dosages disclosed by Hudis et al. because the study of

Henderson et al. is non-analogous art by virtue of not being a dose-dense sequential protocol but a conventional concurrent protocol. This argument is not found to be convincing because there is no reason to believe that the dose-response curve, which indicates the percent of cancer cells killed at a given dosage, is affected by whether a particular drug is administered in a dose-dense or concurrent protocol. The differences observed between dose-desne and non-dose-dense protocols are not the result of any changes in the dose-response curve of the drugs used but rather the result of the same drug, producing the same cell kill percentage, being used more often. In fact, the theoretical rationale for dose-dense chemotherapy, disclosed on pp. 4-6 of the instant specification, rests on the knowledge that, "a given dose always kills a certain fraction, rather than a certain number, of exponentially-growing cancer cells." This statement assumes that the dose-response curve, and thus the percentage of cells killed at a given dose, does not change based on the interval between treatments. Thus the disclosure in the prior art of a particular dose of a chemotherapeutic drug used in a chemotherapy method provides a clear rationale for using the same dose in a dose-dense protocol with the expectation that the efficacy will be the same as it is in the non-dose-dense protocol.

Additionally, Applicant argues that Henderson et al. does not examine the effect of dose escalation of paclitaxel and cyclophosphamide on the effectiveness of these drugs. However, this argument is not convincing because the mere fact that these dosages were used with a reasonable measure of success by Henderson et al. provides

a motivation and reasonable expectation of success for one of ordinary skill in the art to use them.

Furthermore, as stated by Applicant in the amendment submitted August 11, 2006, "the establishment of a dose-response curve, for a particular chemotherapeutic agent, against a particular cancer, is part of the **routine experimentation** that takes place in the field of oncology," and, "the experimentation required to arrive at an optimal dose, for a particular chemotherapeutic agent, against a particular cancer, is **absolutely routine** in the field of oncology." Even assuming, for the sake of argument, that Hudis et al. is considered on its own merits, without the additional teaching of Henderson et al., modifying the specific dosage levels disclosed by Hudis et al. and discovering that the lower dosages disclosed in the instant claims are equally effective is, by Applicant's own reasoning, merely routine and ordinary experimentation which is therefore obvious over the prior art. Therefore, although Henderson et al. has been cited to demonstrate that lower doses of the disclosed chemotherapeutic agents were known in the art at the time of the invention, Henderson et al. is not necessary to repair the defect in the teaching of Hudis et al. and render the instant claims obvious.

For these reasons the argument is not found to be convincing. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL.**

Summary

No claims are allowed in this application. Because Applicant's amendment necessitated the new grounds of rejection introduced in this action, **THIS ACTION IS**

MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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